BACTERIEMIA*

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At the outset of a discussion on disseminated infection in which bacteria have been found in the blood stream, it is well to suggest limitations and to agree upon definitions; for the study of the spread of bacteria may be profitably discussed from many different points of view, and many of the terms used are applied with unlike meanings.

We shall not refer to the technique of the examination of the blood for bacteria.

The review of the clinical pictures presented in the dissemination of the different species of microörganisms will not be considered, nor the transient bacteremia such as occurs after operation, or manipulation in the male genitourinary tract.

Nor will we discuss the phase in which microorganisms are found in the blood stream in the well recognized diseases, such as typhoid fever, pneumonia, relapsing fever, bacterial endocarditis, etc., except to use some of the information obtained to throw light on the sequence of events in various forms of septicemia.

It is the bacteremia occurring in the course of so-called septicemia, which, I believe I am expected to discuss. And I have taken for granted, that as practitioners of medicine and surgery, you have in mind renewing your acquaintance with some of the well known experiments which throw light on the sequence of happenings in disseminated infections I assume that you will wish to hear the prognosis and the methods of treatment discussed, when positive blood cultures are found in patients lying gravely ill with irregular temperatures, with or without chills, rapid pulse, with or

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without metastatic foci. For to quote Sacquepee, "the idea of septicemia corresponds both to a clinical syndrome of general disease and a biological fact constituted by the presence in the blood of one of the recognized pathogenic germs."

What is likely to happen and what he is to do, is the special concern of the practitioner.

Unfortunately, although septicemia and bacteremia are used in most of the medical writing to-day as interchangeable, they have not always been so used, nor are they consistently so used to-day. In the monograph, by Seitz, on the nature of infection in the 3rd edition of the large "Handbuch der pathogenen Mikroorganismen," published in 1929, there occurs, as in the older editions, the following paragraph: "The two conceptions, bacteremia and septicemia must be sharply distinguished. Bacteremia is purely a passive process in which the bacteria pour into the blood from a focus of infection. The blood serves only as a means of transportation for the bacteria. . . . When the exciting agent is not mechanically transported by the blood, but is actively multiplying in the blood current, then we speak of septicemia."

Such a conception has disadvantages. It takes no account of the great capillary fields which form an important part of the circulatory system, in the liver, spleen and bone marrow. It takes no account of the inability of the clinician to recognize the moment when a bacteremia, in the strict sense, passes over into a septicemia.

The distinction is definitely abandoned by Zinsser in his last edition of his Bacteriology. It is abandoned by most writers to-day. Bacteremia and septicemia are used as synonymous. Each year in the medical writings, articles appear which show this usage. In 1928, for example, in the New England Journal of Medicine, O'Brien reports a case of gonococcus septicemia with recovery, and a case of recovery from anthrax septicemia is reported from the Presse médical. Both instances might have been spoken of as examples of bacteremia.

Without a mental grasp of the sequence of happenings, when the body is infected with microörganisms, it is impossible to consider rationally, either prognosis or treatment, or this distinction attempted in the definition of certain bacteriologists, between septicemia and bacteremia.

There are two papers recording experiments on animals that I think well worth bringing to your attention even if you are already familiar with them.

In experiments, recorded in a paper by Hobo, the material used was fine India ink and the amount used from 2.5 to 3.0 c.c. The particles were the same size or smaller than staphylococci and the solution was injected into the ear veins of rabbits. The visible mucous membranes immediately became dark gray; at the end of ten minutes the color had disappeared. The animals were killed at periods varying from forty-five minutes to seventeen days after injection. At autopsy, the spleen, the bone marrow and the liver were found to be stained black. The other organs and tissues—the lungs, heart, brain, nervous tissue, gastrointestinal tract and the kidneys were unstained. microscopical examination showed in the early stages, particles of India ink in the star cells of Von Kupffer of the liver, the sinus endothelial cells and the pulp cells of the spleen and the endothelium of the capillaries of the bone marrow. In the capillary enlargement of the metaphyses of the long bones the particles were so thickly deposited that it was impossible to recognize the phagocytosis. In the kidneys, clumps of the pigment were to be seen here and there. Scattered through the various organs were mononuclear and polymorphonuclear leucocytes filled with black particles.

The precise and interesting experiments made by Wyssokowitsch over forty years ago are equally interesting. He used fresh cultures of moulds, saprophytic, pathogenic and non-pathogenic bacteria and experimented on dogs, rabbits and guinea-pigs. Relatively large quantities were injected into a vein; blood was then drawn at intervals of from ten minutes to twenty-four hours; cultures were

188

taken and the colonies counted. Enormous quantities of spores of moulds (aspergillus and pencillium) and saprophytic bacteria disappeared with astounding rapidity. Within three hours, millions of bacilli (Bacillus subtilis). injected intravenously, had completely disappeared. Bacteria, pathogenic for man, but harmless for the animals experimented on, disappeared in the same way. Thirty minutes after the injection of millions of cocci (Streptococcus pyogenes) into the circulation of a dog, only one colony was found in the blood culture: in one and a half hours the blood drawn was sterile. Even after injections, repeated each day for four days, of many millions of microorganisms (Micrococcus tetragenus) into the blood of rabbits, only six colonies had grown from the blood culture at the end of twenty-four hours. The disappearance of bacteria pathogenic for the animal, injected in small quantities, was equally rapid. In some instances it was complete: that is, the blood withdrawn from a rabbit, into the blood stream of which anthrax bacilli had been introduced. showed no organisms at the end of twenty-four hours. larger doses were introduced, there was first a diminution, then an increase, until the bacteria became countless. a rabbit injected with a large dose of anthrax bacilli, at the end of five minutes, only fifteen colonies were found in the withdrawn blood. At the end of two and a half hours there were no colonies: at the end of forty-six and a half hours, three colonies: at the end of seventy hours, fifty-six colonies: at the end of eighty-four hours, death followed with countless numbers of bacteria in the blood stream. The animal in which no organisms were found in the blood at the end of twenty-four hours, was killed. Cultures from the blood showed no growth; however forty-five colonies grew from a culture taken from the spleen and countless colonies from the liver. In animals that died after an injection of large doses of pathogenic organisms, autopsies regularly showed not only the liver, spleen and bone marrow, but all the tissues swarming with bacteria. The blood itself, in the larger vessels, contained but a small part of the myriads of microbes found throughout the body.

These two experiments show:

- (1) That inert particles the size of bacteria rapidly disappear when introduced into the circulating blood and are found deposited, for the most part, in the liver, spleen and bone marrow.
- (2) Nonpathogenic organisms are deposited in the same way and are destroyed.
- (3) Pathogenic microörganisms in moderate doses are similarly destroyed, but, when more virulent, or in larger doses, multiply in these situations and invade the blood stream; first a few, finally in countless numbers.

The well known sequence of events in infection by spirochetes is also an aid in forming the picture of disseminated microparasites. The course of the disease in rat-bite fever, relapsing fever, syphilis and infective jaundice, show various phases: a latent period, sudden onset of severe symptoms, dissemination in the blood stream, and multiple transitory lesions and finally, disappearance of the microparasites and destructive lesions.

In experimental syphilis in the lower monkeys, even when there are no general manifestations, examination of the pulp of the spleen, the liver and the bone marrow after death, shows abundant treponemata even when the animal, during life, was apparently in perfect health.

Dissemination takes place from germs multiplying in these regions; the liver, the spleen and the bone marrow.

General infection by bacteria follows the same sequence.

By the time the general invasion occurs, the body has acquired a heightened capacity for destruction of the microparasites. The body's reaction to the invading microparasites has altered both locally and generally. The violent reaction, made evident clinically by fever, is an evidence of the destruction of the multitudes of microparasites. If the body cells hold in check the microbes, then a third stage is reached, with local lesions in the body and a more pro-

190

nounced reaction. The blood becomes powerfully bactericidal to the organisms causing infection, microörganisms entering the circulation are rapidly destroyed.

In most infections there is an initial lesion at the point of implantation indicating a local sensitization of the body and a heightened capacity on the part of the cells to react to the invading parasite.

There is a period of generalization when microorganisms are multiplying in the body and invading the blood stream, terminated by widespread destruction of the disseminated parasites.

There is a final period, after the microbes have disappeared from the blood, when local lesions appear from the settling out of the microbes at points of diminished resistance. These periods pass into one another and overlap one another, and are often made indistinct by reinfection and secondary infection.

When a lesion has become established in, or on, the walls of some portion of the circulatory system, during the final period, microörganisms may be poured into the circulating blood and time after time be destroyed.

A few clinical examples will illustrate these points.

Bacterial contamination of the blood stream is not infrequent following infections of the middle ear. The mastoid cells are in close proximity to the lateral sinus. It has long been recognized that infective thrombophlebitis occasionally follows infection here, either by direct involvement of the walls of the sinus or by extension to the sinus through one of the minute communicating veins and that such involvement is made evident clinically by chills and fever. Cultures taken during these periods very frequently show the presence of streptococci in the blood stream. The prompt ligation or removal of the infected vein stops the process and the patient recovers. Although large numbers of pathogenic streptococci have been poured into the blood, they disappear completely and the patient recovers if the

bacterial showers stop spontaneously or are cut off. The blood is bactericidal; the body cells destroy the microörganisms. I asked, not long ago, a distinguished and able otologist, who has ligated or excised the interjugular many scores of times, what had become of the hundreds of thousands of bacteria that had already poured into the blood stream before the infected vein was shut off, and he said he had not the slightest idea.

These patients present examples of bacteria disseminated in the blood stream by lesions in the vascular system, after the body has acquired an altered reaction, a heightened capacity for the destruction of the microörganisms causing the infection. If untreated, unless the primary lesion is very small, the bactericidal power of the blood gradually becomes less and less, the bacteria live longer in the blood, they gain a foothold in various parts of the body, myriads are finally poured into the blood stream and the patient succumbs.

A very different picture is seen in the following case report: A woman caught her wedding ring on some object and tore her finger badly. The wound was sutured. She entered the hospital with gangrene of the finger. Her temperature on admission was 99; the next morning the temperature was normal. The gangrenous finger was amputated, the skin closed except about the exit of a small drain. The first forty-eight hours after operation the temperature was $99\frac{1}{2}$ to $100 \ 3/5$. At eight P. M. on the second day the temperature was $100 \ 1/5$. It then rose until her death at noon of the third day. Cultures from the heart's blood showed streptococcus hemolyticus.

In this instance, before the finger was amputated, streptococci had passed into the circulating blood. The virulence of the streptococci, or the lessened resistance was such, or, to put it in another way, the lessened capacity for bacterial destruction was such, that they gained foothold in spleen, liver and bone marrow, and invaded the blood stream.

Osteomyelitis furnishes another instructive clinical pic-Staphylococcus osteomyelitis is one of the lesions of staphylococcus septicemia. At the beginning of the disease the blood culture is usually positive. The sequence of happenings is often as follows: A child has a small furuncle or small infected wound. After several days or weeks, often when the initial lesion has healed, there is a violent general reaction, chill, fever, prostration. Staphylococci are found in the circulating blood and purulent foci appear in various parts of the body, especially in the expanded position of the shaft near the epiphyseal line where the experiments of Hobo show particles of carbon were deposited in the largest amount.

One sees patients in whom osteomyelitis is only one of many purulent lesions found in the body, others in whom only a single bone is involved, and still others in whom two or more bones are involved. Moreover, when the microorganisms are arrested and start to grow, they may set up a marked lesion in one place and a very slight one in an-Finally the circulating cocci disappear from the blood and localized lesions occur with death of tissue. give briefly a clinical history: A boy two years old was operated on for a painful swelling over his third metacarpal bone. He presented the usual picture of chronic osteo-His history was as follows: Eight months bemvelitis. fore he had had a phlegmon following an infected wound on his forehead. After this he became very ill with signs of broncho-pneumonia, which was followed by an abscess on the back of his hand in the region of the present swelling and in the lateral thoracic region. A positive blood culture showed Staphylococcus aureus. The abscess on his hand and the one in the lateral thoracic region were incised and cultures of Staphylococcus aureus were obtained. He developed evidences of pericarditis; 18 c.c. of purulent fluid growing staphylococci were aspirated; ascites appeared. Aspiration showed straw colored serum; cultures were negative. The patient had had an acute staphylococcus sepsis with an abscess in the subcutaneous tissue, purulent pericarditis and osteomyelitis. At operation eight months after the onset the usual signs of chronic staphylococcus osteomyelitis were present. The various foci in the body had healed; only where the lodged cocci had caused gross tissue death did infection persist. After removal of the necrotic tissue, the patient recovered. Seen nine months later he was in perfect health, fat and rosy. A year later a staphylococcus abscess was opened in the shoulder region and after several weeks healed. At present he has a painful area over the middle shaft of the humerus. The X-ray shows thickening of the periosteum at this point. He has a low grade residual infection of the humerus.

The illness of the King of England was given wide publicity and furnishes another clinical picture. He suffered from a streptococcic septicemia which finally localized in the base of the right lung and which was followed by empyema. A rib was resected and he has slowly recovered. To quote from the London letter in the Journal of the American Medical Association: "In the first phase of this severe illness, gradual in its onset, there were noted general infection with imperfect localization; little or no cough and only one small patch of pleuritic friction; a blood culture positive for streptococcus, and an irritative state of the nervous system which produced profound distress and a sense of illness. Toward the end of the first phase came an accentuation of pleuritic friction, which extended into the diaphragm. The second phase was one of increasing toxemia with dusky appearance, dry cracked tongue, periods of delirium and exhaustion—in short, a clinical picture resembling that of severe typhoid in the third and fourth week, but with the added anxiety of attacks of dyspnea and cyanosis due to strain on the heart. With the next phase came an abatement of fever and some evidence of localization. The blood culture was now negative, and toxemia was less with delirium subsiding. localization in the right lung did not result at this stage in effusion as was shown by puncture and excellent roentgenograms. A few days later the temperature rose rather abruptly to a higher level, and on December 12 there was 194

evidence at the extreme right base of an effusion which had begun between the lung and the diaphragm. Drainage by means of rib resection was performed on the same day under general anesthesia—gas, oxygen and ether. The prominent organism in the empyema was found to be identical with the streptococcus found in the blood."

It is unnecessary to give further examples. Our conception of septicemia, built up by clinical observations made when pathogenic bacteria are detected in the circulating blood, must take into account all these cases. Examination of the contaminated blood gives but small indication of the complex phenomena taking place. The number of microbes discovered may be but a portion of the myriads in the body or may only indicate the passage of hundreds of thousands on their way to destruction.

The forecast of the patient's fate can only be made by considerating the entire clinical history in connection with the blood culture.

It is not necessary to be hopeless when pathogenic germs are found in the blood current. In many patients the germs are poured into blood powerfully bactericidal. In many the germs are found in early stages of disseminated infection, which will pass on to localization and recovery.

The outcome in any given case depends on the number and virulence of the bacteria, the resistance of the host and the character of the focal lesions.

An attempt might be made to base an opinion on the number of colonies found in the blood cultures. It is self-evident that a single colony found on a single plate must have a different significance from hundreds of colonies found on every plate, but only by repeated examinations and a comparison of a number of similar cases can an indication be given regarding prognosis, and whether or not the bacteria are pouring into the blood stream with bactericidal properties, or are multiplying in the liver, spleen and bone marrow.

These facts also furnish a guide for intelligent treatment.

Obviously, proper nursing, rest, administration of fluids and careful observation are measures applicable to all severe illness. I shall only refer to measures especially called for in septicemia.

The ligation and excision of a vein, the seat of suppurative thrombophlebitis, if done early, is a most satisfactory measure. Here, as we have said, the bacteria are passing into a blood stream which has bactericidal properties, shutting off further contamination.

Unfortunately there is only one region in the body where the anatomical relation and arrangement of the infected area and the tributary veins offer suitable conditions for surgical interference. I refer to the mastoid cells, lateral sinus and jugular vein.

There were ten recoveries and three deaths in a series reported from the otological service of St. Luke's Hospital. In the ten patients that recovered, eight had the jugular ligated immediately after the streptococci were discovered in the blood. There were two patients that recovered without ligation; in one there was only a single culture showing one colony. Two were instances of severe blood stream infection with hemolytic streptococci. Both recovered after ligation.

A similar condition occasionally occurs in an area of infection in an extremity. Amputation above the infected area is followed by complete and startling recovery. An observation of Dehelly is interesting. He amputated the leg of a fireman for an infected compound fracture. The patient continued ill and repeated examination showed hemolytic streptococci in the blood. He reamputated through the thigh. The patient promptly recovered. Thereafter the blood cultures were negative. A most painstaking examination of the amputated stump showed suppurative thrombophlebitis of a single vein.

In puerperal sepsis the effort to remove the uterus with the ovarian veins which at times show suppurative thrombophlebitis has met with little success. In most instances we are dealing with a suppurative thrombophlebitis occurring in the early stages of dissemination.

In infection of the lips and face with suppurative thrombophlebitis, both the jugular and facial have been ligated to prevent dissemination. Lexer reported a case of carbuncle of the cheek in which there was a purulent thrombophlebitis of the facial and general infection and in which he was able to avoid further metastases and cure the patient by ligation of the jugular.

Two years ago Roeder reported a case in which he records ligation of the angular vein in an infection of the upper lip. The vein was not thrombosed, culture of its walls and lumen were negative. There were no positive blood cultures. The measure was said to be prophylactic. There is nothing to indicate that the patient would not have recovered without ligation.

Attempts have also been made to excise the initial lesion under the impression that the microörganisms are finding their way into the circulation from this primary focus. Such treatment is nearly always unsuccessful, often harmful. The microörganisms found in the blood stream are usually the organisms multiplying far from the site of inoculation.

The study of the treatment of anthrax serves as an illustration. Twenty-four years ago the text books of surgery advised excision of the skin lesion of anthrax, followed by the application of caustics, strong antiseptics, or the actual cautery. Small local lesions recovered after this treatment but the results were not as good as when the lesions were protected from injury, the parts kept at rest, and secondary infection avoided. Apparently in some instances the bacilli seem to have been disseminated by the operation. During the last ten years a powerful antianthrax serum has been available and has been used with

and without excision. There is a growing recognition that the disease is often local and shut in by a barrier of cells; that excision may break through this barrier and disseminate the bacilli and may cut out a focus perhaps furnishing antibacterial substances; and that, if the microörganisms are widespread, as is often the case, local excision is useless.

The following English statistics of the Ministry of Health published in 1921 are interesting:

	Cases	Deaths	Mort.P.C.
Serum alone	200	8	4.
Excision only	397	44	11.1
Excision and serum	174	25	14.4
No special treatment	29	14	28.3

The secondary lesions that appear early in dissemination are the result of bacteria deposited in special sensitized areas or in areas of least resistance or areas that offer anatomical arrangement unusually favorable for the growth of the microörganisms.

Incision or evacuation of exudate in these instances can have only an indirect effect on the microörganisms in the circulation. Such foci are the result of dissemination, not the cause.

It is a common observation and one confirmed by experience that mechanical interference, during the early stage of infection should be confined to the simplest measures, such as aspiration and simple incision to afford drainage and thus avoid unfavorable pressure from the exudate. It is only after the bacteria have disappeared from the circulation and the local focus is well circumscribed, that incision and drainage show satisfactory results. This was well shown in the streptococcus infections that occurred in several of the camps during 1918. Extensive operation on the chest when there was a thin turbid exudate in the pleura and streptococci in the blood showed high mortality. These patients were suffering from streptococcus septicemia as the multiple lesions at autopsy showed.

Aside from these purely surgical measures which can only be applied in special cases with localized lesions, there are certain general measures in use to-day, such as bacteriotherapy, serotherapy, chemotherapy and the transfusion of blood. My own experience in these fields is limited and my attitude sceptical. I have seen no such convincing evidence of the efficacy of any measure suggested as to feel justified in advocating it whole-heartedly. I shall review therefore a few of the reports published during the last two years. In 1928, Cadham reported the history of eighteen patients with septicemia treated with repeated inoculations of a homologous immune animal serum and repeated transfusions of human serum, with sixteen recoveries and two deaths. The next year Prof. Vincent, of Paris, reported very favorably on a new anti-streptococcus serum, and Dujol, in the same year, reported recovery from a staphylococcus septicemia, after injection of an auto-vaccine prepared from fluid containing pus and staphylococci withdrawn from the pericardium. In January of this year Rosher reported in the Lancet, four cases of streptococcus septicemia in which Streptococcus hemolyticus was isolated from the blood and in which complete recovery followed treatment with scarlet fever streptococcal antitoxin, and several weeks before Burt-White reported twentyseven cases with a morality of 29.6 per cent treated in the same way.

I shall offer, after the discussion of the introduction of chemicals into the circulation, reasons for not accepting too readily, the conclusions drawn from these favorable reports.

During the war, Anderson and Richardson, in the *British Journal of Surgery* of 1917 and 1918, reported favorable results from intravenous injection of eusol, one of the preparations of hypochlorite of soda. During the last twelve years similar reports have followed the introduction, intravenously, of other antiseptics; perhaps the best known is mercurochrome. About the time of its introduc-

tion wide publicity was given to the astonishing, or as they were then described, truly wonderful results.

It is well known that valuable as antiseptic solutions are in preventing secondary infection, in sterilizing the skin, instruments etc., there are reasons why their use, when bacteria have become established and are multiplying in the body, is unsatisfactory:

First, any chemical substance which kills bacteria when brought in contact with them outside the body acts by some sort of reaction between the chemical and the protoplasm of the bacterium, an analogy existing between the ordinary chemical reaction between two reagents and the reaction between the antiseptic and the bacterium. The reaction is by no means simple, nor is it the same for the different chemicals, but in all cases it is connected in some way with damage to the surface of the bacterium so that it cannot carry on the normal exchange on which its life depends.

Second, the antiseptic has a tendency to combine with substances other than the bacterium with which it comes in contact. Therefore, the living cells, the various chemical ingredients and albumins in the body unite with the antiseptic.

Third, the antiseptic, just as any chemical, is used up and rendered inert by combining with the various substances with which it comes in contact.

Fourth, to be effective, the antiseptic must come in contact with the body of the bacterium. That is, a germ inside a cell is not killed by the antiseptic if the chemical combining property on which its activity depends is quenched before it reaches the body of the germ.

Fifth, the active cells on which the destruction of the bacteria depend are more delicate than the bacterium. Their surface condition, on which their normal function depends, is even more liable to be affected in a harmful manner than the surface of the bacterium by chemical solutions; the living cells, even if not killed, may be damaged.

All these considerations make it improbable that any antiseptic applied with the idea that it is a simple germicide will be effectual. Notwithstanding these facts, which have been brought out by careful and patient studies, very favorable results continue to be reported from the intravenous injection of antiseptics. In 1930, Harris reported in the United States Veterans Bureau Medical Bulletin. that a patient recovered after nine intravenous injections of mercurochrome. The patient was suffering from Streptococcus viridans septicemia. The same year Veillon reported in the Bulletin de Soc. méd. des hôpitaux, recovery from meningococcus septicemia after three injections of acriflavine hydrochloride solution. In August, 1929, Bernstine reported sixteen cases of blood stream infection in which metaphen, introduced intravenously, had a beneficial effect. All were cases of puerperal septicemia.

The difficulty in interpreting these results is that each case quoted must be carefully studied and analyzed by itself. For example, the cases reported by Dujol as recovering after administration of autogenous vaccine are similar to the one I have reported as recovering without vaccine. Did the patient reported by Harris recover on account of the nine injections of mercurochrome or in spite of it? One case report does not furnish proof of the efficacy of a given form of treatment.

As I have said, there has been as yet, no general recognition of the curative value of any of these measures, yet one cannot dismiss without comment the evidence of sudden and rapid recovery presented in many of the case reports. In certain instances there is evidence of severe disturbances after the introduction of chemicals and after the introduction of serum. Is some form of protein shock a common factor, either from the serum introduced or from damage to body cells by the chemicals? Is the protective mechanism of the body stimulated or reactivated? As one watches the case reports year after year, one is surprised by the similarity of the results from widely different measures and widely different chemicals. Obviously it is diffi-

cult to estimate the value of treatment where such different conditions are grouped together under a single term, and where the sporadic nature of the disease makes the numbers that come under the observation of one observer so limited.

In regard to transfusion of whole blood, there does seem to be a general agreement that it is beneficial, at least temporarily, especially in subacute and chronic cases. Repeated small transfusions seem to be more effective than a single large one. The color improves, the feeling of well being returns, the appetite improves; it seems difficult not to believe that it is helpful in aiding the body to combat disseminated infection.

I have endeavored, in this cursory talk, to interest you in the phases in the course of infection, and to bring to your attention the necessity of bringing a critical attitude (founded on a knowledge of, one might say, the vagaries of septicemia) toward the various measures that are enthusiastically advocated, often perhaps, to the detriment of the patient.

There seems to be a widespread, although erroneous impression that a patient in whose blood streptococci or staphylococci are found is doomed to death. Therefore recovery following any form of treatment is set down as extraordinary and the agent used extolled.